REMARKS

Claims 1, 3-19 and 21-24 are pending.

Claim Rejections under 35 USC § 112

Claims 1, 3-19 and 21-24 rejected under 35 USC § 112 ¶1

The Examiner believes Claim 1, as amended in Applicants last Office Action response, contains new matter and that there is no support for the claim as recited. The Examiner rejected incorporating the limitation "from greater that" 20 to "less than or equal to" 80% The Applicants respectfully disagree. The Examiner believes the "specification only recites concentrations from 10 to 80%, preferably from 20 to 60%" and therefore, there is "no support for claiming from greater than 20% excluding ranges of the prior art." The Applicants argue that even though the term "greater than" was not explicitly disclosed, amounts greater than 20% are automatically included in the disclosed ranges. Applicants have satisfied the burden of showing the upper limit of a range comprising "greater than" 20% by including the term "less than or equal to" 80%. Claim 1 has an upper limit, as required by MPEP 2163.05 III, and thusly, the recited range does not cause the claim to read literally on embodiments outside the recited range of "10% to 80%, preferably from 20 to 60%" and as such, support for Claim 1 is provided by the Specification.

Claims Rejections under 35 USC § 102

Claims 1, 3-19 and 21-24 rejected 35 USC § 102(b)

Claims 1, 3-19 and 21-24 are rejected under 35 USC § 102(b) as being anticipated by US 6,066,334. The Examiner states US 6,066,334 shows a composition comprised of a binder wherein the binder is a mixture of polyvinyl acetate and polyvinylpyrrolidone in an amount of .5% to 20 %.

Anticipation can only be established by a single prior art reference which discloses each and every element of the claimed invention. *RCA Corp. v. Applied Digital Data Systems, Inc.*, 730 F.2d 1440, 1444, 221 USPQ 385, 388 (Fed. Cir. 1984). The identical invention must be shown in as complete detail as it is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The Examiner has failed to meet this burden.

Applicants argue the instant invention discloses a time released which is not taught by US 6,066,334. According to the instant invention components a)-d) of Claim 1 are comprised in the dosage forms in such a way that the resulting dosage forms show delayed release. The dosage forms according to US 6,066,334 may contain the same component (e.g. a formulated mixture of polyvinyl acetate and polyvinyl pyrrolidone), but according to this prior art reference, the component is formulated in such a way that the resulting dosage forms show rapid or immediate release of the active ingredient. This rapid release, as taught in US 6,066,334, is caused by the overall composition of the formulation which preferably only contains up to 15 % of the formulated mixture of polyvinyl acetate and polyvinyl pyrrolidone in combination with other additives. According to examples 3, 4, and 5 of US 6,066,334, from 98.8 to 99.5 % of the active ingredients are released after 30 minutes. The aforementioned immediate release in less than 1 hour cannot be understood by one of ordinary skill in the art as "delayed release." The Examiner is directed to Gundert-Remy et al. (*Oral Controlled Release Products Therapeutic and Biopharmaceutic Assessment*, 1990) and USP 23 1880 (*General Information In Vitro and In Vivo Evaluation of Dosage Forms*; both cited references enclosed) wherein "delayed release" and "immediate release" are defined terms and are terms that one of ordinary skill in the art would well know and understand. The Examiner is directed to tables 2, 4 and 6 of the instant application wherein a time course of up to sixteen hours is required for a major portion of the active ingredients to be released. A release pattern such as disclosed in the instant invention falls well within the definition of "delayed release" as known to one of ordinary skill in the art.

Since US 6,066,334 does not teach each and every element of Claim 1 it does not anticipate Claim 1. Applicants therefore respectfully request withdrawal of the rejection under 35 USC § 102(b).

Claims Rejections under 35 USC § 103

Claims 1, 3-19 and 21-24 rejected 35 USC § 103(a)

To establish *prima facie* obviousness, the examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable expectation for success in doing so, and a teaching or suggestion of each claim element (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ 2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka,*

490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

The Examiner has not made the required showing.

Claims 1, 3-19 and 21-24 are rejected under 35 USC 103 (a) as being unpatentable over the combined disclosures of US 6,066,334 and US 4,837,032. The Examiner believes one of ordinary skill in the art would be motivated to combine the greater amounts of polyvinyl pyrrolidone and polyvinyl acetate of US 4,837,032 with the active agent of US 6,066,334.

The Applicants respectfully disagree. One of ordinary skill in the art would not expect that using a formulated mixture of polyvinyl acetate and polyvinyl pyrrolidone would lead to dosage forms with delayed release, as disclosed in the instant invention. US 6,066,334 expressly teaches dosage forms with rapid release as described above. US 4,837,032 discloses tablets with extended release which may be obtained by using polyvinyl pyrrolidone and polyvinyl acetate but US 4,837,032 does not teach or suggest a formulated mixture. The Examiner has argued that it would have been obvious to use increased amounts of the polymer combination of US 4,837,032 to provide delayed release for US 6,066,334. However, it is not a reasonable expectation by one of ordinary skill in the art that the use of increased amount of a binder previously disclosed in US 6,066,334 for rapid release dosage forms would lead to the delayed release disclosed in US 4,837,032. The distinctive release patterns of the instant invention are due to the overall formulation of the dosage forms and not merely to the presence of the mixture of polyvinyl acetate/polyvinyl pyrrolidone.

For the reasons expressed above, it is urged that the prior art references cited by the Examiner either singly or in combination fail to anticipate or suggest the present invention as defined by the Claims. Accordingly, a *prima facie* case of obviousness has not been established by the Examiner, and the rejection under 35 USC § 103 should be withdrawn.

ATTACHMENT A

Paperback APV

Die Buchreihe wird im Auftrag der Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. (APV), Mainz, herausgegeben.

Band 21

In der Reihe Paperback APV sind bereits erschienen:

Oral Controlled Release Products

Therapeutic and Biopharmaceutic Assessment

Edited by

Prof. Dr. U. Gundert-Remy
Bundesgesundheitsamt, Berlin

and

Priv.-Doz. Dr. H. Möller
Hoechst AG, Frankfurt

with 83 figures and 9 tables

WVG
Wissenschaftliche Verlagsgesellschaft mbH Stuttgart 1990

In this chapter the requirements for studies "in vivo" will be compared and discussed. Paragraphs on study of release characteristics "in vitro" and their possible correlation with "in vivo" results have been treated elsewhere. It should only be added here that most guidance documents contain – if any – only cursory reference to "in vitro" studies. The Japanese guideline and the USA draft only give more attention to it. Ideally it should constitute a part of every C/MR guidance text.

2. Definitions

Before starting discussions, it may be useful to give some definitions. According to the USP XXII (2) and replacing the ambiguous word "drug" by "active substance" the following definitions apply:

Modified-release (MR) dosage forms are defined as those for which the active substance release characteristics of time-course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

This and the following definitions and terminology are also used in the EC Note for Guidance mentioned above. In this definition conventional products are pharmaceutical products designed for (almost) immediate release (IR), like tablets, capsules, syrups. "Modified-release" as defined in the USP corresponds to "controlled-release" in FDA terminology. In the present chapter "controlled/modified release" (C/MR) is used throughout in view of international harmonization and to express both aspects of these formulations. In USP XXII only two types of MR-products are defined: extended-release (ER) and delayed-release (DR).

An extended-release (ER) dosage form is defined as one that allows at least a two-fold reduction in dosing frequency as compared to that active substance presented as a conventional dosage form.

A delayed-release (DR) dosage form is defined as one that releases (the bulk of) an active substance at a time other than promptly after administration.

For practical purposes, i.e. the distinction between SR products and other products with only a marginally slowed-down release rate in the EC guidance another category is mentioned which may be defined as follows:

A *slow-release* (SR) dosage form is defined as one that releases an active substance more slowly than its conventional form, but not to such a degree that it allows an appreciable reduction in dosing frequency.

The pharmacokinetic characteristics of these three types of products are described in an appendix to the EC guidance on prolonged-action forms as represented in table 1.

Table 1: Types of Controlled/Modified Release Products

	C_{max}	t_{max}	terminal elimination half-life
SR:	lower	later	unchanged
ER:	lower	later, often ill defined	apparent elimination half-life prolonged
DR:	unchanged	lag time & later	essentially unchanged

Für uns gültig: SR + ER

3. Overview by comparison

An overview of guidance documents concerning the same subject, i.e. modified release products, is only sensible if it constitutes a comparison. In this case a comparison of Australian (3), Canadian (4), EC (1), Japanese (5), Nordic (6) and USA (7) texts. A comparison of guidance documents on C/MR products however is not easy. They differ not only in terminology, lay-out and degree of detail, but also in content and underlying philosophy.

The framework of this chapter does not allow an exhaustive comparison. For an effective comparison the texts will be cut up in several elements according to a scheme recognizable in most C/MR guidance texts, especially in the most concise of them, the Nordic one (table 2). Based on this scheme the primary requirements will be described and compared. Aspects of C/MR guidance in common with other bioavailability guidance are not discussed. They do not bring in new aspects. Inescapably this large scale comparision will bring with it some loss of nuance.

4. Preambles and introductory paragraphs

The introductory text of guidance documents may betray the way of thinking of the regulatory agency, and so give an extra clue to the applicant. Most preambles contain however only generalities which nobody will deny. The C/MR guidance of Australia and the Nordic Council is inserted into general bioavailability guidance and their preambles do not contain special reference to C/MR products. Really worth mentioning is the first paragraph of the Japanese guideline (5). It gives an overview of all aspects to be considered in their mutual relations. It is gratifying to read how besides pharmacokinetics – generally overrepresented in C/MR guidance – due attention has been given to the physico-chemical and physiological basis on one hand, to the pharmacodynamics and its clinical correlates on the other. In a sense it is an

are available. The reference materials of a drug substance may be relatively impure. Limits for the purity of a drug substance are set to indicate drug quality. The setting of limits on related substances and process contaminants can be characterized as follows.

(1) Limits are set on total impurities, and an upper limit may be set on any single impurity. The limit for total impurities should maintain, if possible, a nominal composition material balance.

(2) Impurity profiles are documented. These are profiles of the lots of drug substances used in clinical studies and in toxicological studies that establish the safety of drug substances. The lots used in these studies should be typical products of the manufacturing process in use at that time.

(3) Limits for residual solvents are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.

(4) General inorganic contaminants are monitored by appropriate tests such as a heavy metals limit test and/or a test for residue on ignition. Traditional compendial limits are applied unless otherwise indicated. Specific metal contaminants that appear during manufacturing should be monitored by appropriate analytical techniques, and limits should be set based on the toxicological properties of these metals.

(5) Appropriate limits are set for impurities known to be toxic.

(6) If appropriate, enantiomeric purity is controlled.

Although water is not classified as an impurity, limits for water content may be needed to ensure the stability or ease of processing a drug substance.

NDA Filing—During the IND phases of drug development, the manufacturing process for a drug substance may undergo a number of revisions. Generally, the scale will have changed from laboratory size and will approach or reach full production batch size. A number of batches will normally have been produced, and a historical data base of the results of testing for impurities will exist. When significant changes in a manufacturing process are made, the impurity profile should be reviewed to determine if the toxicological studies are still supportive.

At the NDA stage a reference standard of defined purity is available, analytical methods have been validated, impurity and degradation profiles are known, and enantiomeric purity has been evaluated. The setting of limits on related substances and process contaminants can be characterized as follows.

(1) Consistency of the impurity profile of a drug substance has been established.

(2) IND limits for total and individual impurities (identified and unidentified) are reviewed and adjusted based on manufacturing experience and toxicological data.

(3) Impurities present in significant amounts are identified and individual limits are set. However, it is not always possible to identify and/or prepare authentic substances for impurities. The labile nature of some impurities precludes this possibility. Limits may be set on these substances based on comparison of lots produced and used in toxicological and clinical studies.

(4) The impurity profiles of the lots designated for marketing should not be significantly different from those of the lot(s) used for toxicological and clinical studies.

(5) The composition material balance should be used, if possible, to evaluate the adequacy of the controls.

(6) Limits for residual solvents are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.

(7) Limits are set for inorganic contaminants by appropriate tests such as a heavy metals limit test and/or by a test for residue on ignition. Traditional compendial limits are applied unless otherwise indicated. Based on toxicological properties, limits may be set for specific metal contaminants that appear during manufacturing.

Post NDA Approval—After approval and marketing of a pharmaceutical product, significant changes may be made in manufacturing the bulk drug substance. There may be technological, ecological, economic, or safety reasons for these changes. If they occur, the Pharmacopeial and NDA impurity limits and rationale should be reviewed; the limits should be revised when indicated to ensure similar or improved quality of the drug substance.

ANDA Filing—The drug substance for a pharmaceutical product eligible for ANDA status normally is an official article and should be well characterized analytically. Drug substances are typically available from multiple sources, and each source may have a different manufacturing process. [illegible] is essential that the dosage-form manufacturer evaluate each supplier's drug substance impurity profiles. Limits can then be set based on the more detailed concepts described for NDA filing, including review of compendial monographs for appropriateness.

⟨1088⟩ IN VITRO AND IN VIVO EVALUATION OF DOSAGE FORMS

The Pharmacopeia provides for dissolution and drug release testing in the majority of monographs for solid oral and transdermal dosage forms. In recognition of the sensitivity of dissolution tests, where a valid bioavailability-bioequivalence (BA-BE) study is in hand, the policy of this Pharmacopeia has been to give this information dominant consideration in setting dissolution standards. Early practice was to develop dissolution requirements based on the in vitro performance of clinically successful formulations. Similarity in dissolution behavior has long been sought from the perspectives of both bioavailability and quality control considerations.

It is the goal of the pharmaceutical scientist to find a relationship between an in vitro characteristic of a dosage form and its in vivo performance. The earliest achievable in vitro characteristic thought to portend an acceptable in vivo performance was tablet and capsule disintegration. A test for disintegration was adopted in *USP XIV* (1950). At that time, no quantitative work was done in attempting to demonstrate such a relationship, especially in regard to in vivo product performance. However, advances in instrumental methods of analysis ultimately opened up prospects for this work. The disintegration test was recognized as being insufficiently sensitive by the USP-NF Joint Panel on Physiologic Availability, and in 1968 the Panel directed the identification of candidate articles for the first twelve official dissolution tests that used *Apparatus 1*.

The state of science is such that conduct of in vivo testing is necessary in the development and evaluation of dosage forms. Also, no product, including suspensions and chewable tablets, should be developed without dissolution or drug release characterization where a solid phase exists. This chapter sets forth, for products intended for human use, guidelines for characterizing a drug that include: (1) developing in vitro test methods for immediate-release and modified-release dosage forms, (2) designing in vivo protocols, and (3) demonstrating and assessing in vitro–in vivo correlations for modified-release dosage forms.

IN VITRO EVALUATION

Dissolution and Drug Release Testing—Method Development for Immediate-release Dosage Forms

Dissolution testing is required for all solid oral Pharmacopeial dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect. Exceptions are for tablets meeting a requirement for completeness of solution or for rapid (10 to 15 minutes) disintegration for soluble or radiolabeled drugs. The apparatus and procedure conform to the requirements and specifications given in the general chapter *Dissolution* ⟨711⟩. Generally, experiments are conducted at 37°.

The dissolution medium preferably is deaerated water or, if substantiated by the solubility characteristics of the drug or the formulation, a buffered aqueous solution (typically pH 4 to 8) or a dilute acid (0.001 *N* to 0.1 *N* hydrochloric acid) may be used. The usual volume of the medium is 500 to 1000 mL, with the use of greater volumes (up to 2000 mL) allowed for drugs having limited solubility. The quantity of medium used should be not less than 3 times that required to form a saturated solution of the drug substance. The significance of deaeration of the medium should be determined. Addition of solutes (i.e., surfactants) and electrolytes to aid in solubilization of the drug must be balanced against the loss of the discriminatory power of the test. The use of hydroalcoholic media is generally not favored. The use of such media should be supported by a documented in vitro–in vivo correlation. Conversely, it should be recognized that this discriminatory power could in some circumstances be excessive if

that it may result in detection of differences in dissolution that are not clinically significant.

The choice of apparatus should be based on knowledge of the formulation design and actual dosage form performance in the in vitro test system. Since dissolution apparatuses tend to become less discriminating when operated at faster speeds, lower stirring speeds should be evaluated and an appropriate speed chosen in accordance with the test data. The most common operating speeds are 100 rpm for *Apparatus 1* (basket) and 50 rpm for *Apparatus 2* (paddle) for solid-oral dosage forms and 25 rpm for suspensions. A 40-mesh screen is used in almost all baskets, but other mesh sizes may be used when the need is documented by supporting data.

Apparatus 2 is generally preferred for tablets. *Apparatus 1* is generally preferred for capsules and for dosage forms that tend to float or that disintegrate slowly. A sinker, such as a few turns of platinum wire, may be used to prevent a capsule from floating. Other types of sinker devices that achieve minimal coverage of dosage form surface are commercially available. Where the use of a sinker device is employed, it is incumbent on the analyst to assure that the device used does not alter the dissolution characteristics of the dosage form.

Dissolution testing should be conducted on equipment that conforms to the requirements in the chapter *Dissolution* (711) and that has been calibrated with both the USP Salicylic Acid and Prednisone Calibrator Tablets. The method of analysis should be validated in accordance with the procedures given in the chapter *Validation of Compendial Methods* (1225).

The test time is generally 30 to 60 minutes, with a single time point specification for pharmacopeial purposes. To allow for typical disintegration times, test times of less than 30 minutes should be based on demonstrated need. Industrial and regulatory concepts of product comparability and performance may require additional time points, and this may also be a feature required for product registration or approval. For registration purposes, a plot of percentage of drug dissolved versus time should be determined. Enough time points should be selected to characterize adequately the ascending and plateau phases of the dissolution curve.

Dissolution test times and specifications usually are established on the basis of an evaluation of dissolution profile data. Typical specifications for the amount of active ingredient dissolved, expressed as a percentage of the labeled content (Q), are in the range of 70% to 80% Q dissolved. A Q value in excess of 80% is not generally used, as allowance needs to be made for assay and content uniformity ranges.

For products containing more than a single active ingredient, dissolution normally should be determined for each active ingredient. Where a dissolution test is added to an existing monograph, a disintegration test is deleted. However, in the case of sublingual preparations, a short disintegration time may be retained as a monograph specification in addition to a dissolution requirement.

Dissolution and Drug Release Testing—Method Development for Modified-release Dosage Forms

Drug release testing is required for all modified-release dosage forms in which absorption of the drug is necessary for the product to exert the desired therapeutic effect. The apparatus and procedure conform to the requirements and specifications given in the general chapter *Drug Release* (724).

The dissolution medium preferably is deaerated water or, if substantiated by the solubility characteristics of the drug or the formulation, buffered aqueous solutions (typically pH 4 to 8) or dilute acid (0.001 N to 0.1 N hydrochloric acid) may be used. (See above under *Dissolution and Drug Release Testing—Method Development for Immediate-release Dosage Forms*.) For modified-release dosage forms, the pH- and surfactant-dependence of the dosage form should be evaluated by in vitro testing in media of various compositions. The volume of medium will vary depending on the apparatus used and the formulation under test.

The choice of apparatus should be based on knowledge of the formulation design and actual dosage form performance in the in vitro test system. *Apparatus 1* (basket) or *Apparatus 2* (paddle) may be more useful at higher rotation frequencies (e.g., the paddle at 100 rpm). *Apparatus 3* (reciprocating cylinder) has been found to be especially useful for bead-type modified-release dosage forms. *Apparatus 4* (flow cell) may offer advantages for modified-release dosage forms that contain active ingredients having very limited solubility. *Apparatus 7* (reciprocating disk) has been shown to have application to nondisintegrating oral modified-release dosage forms, as well as to transdermal dosage forms. *Apparatus 5* (paddle over disk) and *Apparatus 6* (cylinder) have been shown to be useful for evaluating and testing transdermal dosage forms.

At least three test times are chosen to characterize the in vitro drug release profile for Pharmacopeial purposes. Additional sampling times may be required for drug approval purposes. An early time point, usually 1 to 2 hours, is chosen to show that potential dose dumping is not probable. An intermediate time point is chosen to define the in vitro release profile of the dosage form, and a final time point is chosen to show essentially complete release of the drug. Test times and specifications are usually established on the basis of an evaluation of drug release profile data. For products containing more than a single active ingredient, drug release should be determined for each active ingredient.

Where a single set of specifications cannot be established to cover multisource monograph articles, application of a Case Three standard is appropriate. In Case Three, multiple drug release tests are included under the same monograph heading, and labeling requirements are included to indicate with which drug release test a specific product complies and, in some cases, the biological performance to be expected.

Drug release testing should be conducted on equipment that conforms to the requirements in the chapter *Drug Release* (724) and that has been calibrated with the appropriate USP calibrators. The method of analysis should be validated in accordance with the procedures given in the chapter *Validation of Compendial Methods* (1225).

IN VIVO EVALUATION OF MODIFIED-RELEASE DOSAGE FORMS

In evaluating a modified-release product, a fundamental issue is the types of studies that should be performed to give reasonable assurance of safety and efficacy. While providing important information concerning the release characteristics of the drug from the dosage form, at present in vitro studies are most useful for such purposes as monitoring drug product stability and manufacturing process control. The assessment of safety and efficacy of a modified-release dosage form is best achieved through observing in vivo pharmacodynamics or pharmacokinetics. Moreover, where there is a well-defined, predictive relationship between the plasma concentrations of the drug or active metabolites and the clinical response (therapeutic and adverse), it may be possible to use plasma drug concentration data alone as a basis for the approval of a modified-release preparation that is designed to replace an immediate-release preparation.

The following guidelines are intended to provide guidance in drug substance evaluation and the design, conduct, and evaluation of studies involving modified-release dosage forms. While these guidelines will focus on oral drug delivery systems, the principles may be applicable to other routes of drug administration. (e.g., transdermal, subcutaneous, intramuscular, etc).

Characterization of Drug Substance

PHYSICOCHEMICAL PROPERTIES

Physicochemical information necessary to characterize the drug substance in a modified-release dosage form should generally be no less than for the drug substance in an immediate-release dosage form. Additional physicochemical information may be needed on polymorphism, particle size distribution, solubility, dissolution rate, stability, and other release-controlling variables of the active drug entity under conditions that may react to the extremes of the physiologic environment experienced by the dosage form. For purposes of this chapter, *active drug entity* is taken to be the official drug substance.

PHARMACOKINETIC PROPERTIES

It is recommended to characterize thoroughly the input absorption profile of the active drug entity from a rapidly available